

## University of Groningen

### Overfeeding, autonomic regulation and metabolic consequences.

Scheurink, A.J.W.; Balkan, B; Strubbe, J.H.; van Dijk, G.; Steffens, A.B

*Published in:*  
Cardiovascular Drugs and Therapy

*DOI:*  
[10.1007/BF00120496](https://doi.org/10.1007/BF00120496)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
1996

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Scheurink, A. J. W., Balkan, B., Strubbe, J. H., van Dijk, G., & Steffens, A. B. (1996). Overfeeding, autonomic regulation and metabolic consequences. *Cardiovascular Drugs and Therapy*, 10, 263 - 274. <https://doi.org/10.1007/BF00120496>

#### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

#### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

## Overfeeding, Autonomic Regulation and Metabolic Consequences

Anton JW Scheurink, Börk Balkan,  
Jan H Strubbe, Gertjan van Dijk and  
Anton B Steffens.

Department of Animal Physiology, University of Groningen, Haren,  
The Netherlands

**Summary.** The autonomic nervous system plays an important role in the regulation of body processes in health and disease. Overfeeding and obesity (a disproportional increase of the fat mass of the body) are often accompanied by alterations in both sympathetic and parasympathetic autonomic functions. The overfeeding-induced changes in autonomic outflow occur with typical symptoms such as adiposity and hyperinsulinemia. There might be a causal relationship between autonomic disturbances and the consequences of overfeeding and obesity. Therefore studies were designed to investigate autonomic functioning in experimentally and genetically hyperphagic rats. Special emphasis was given to the processes that are involved in the regulation of peripheral energy substrate homeostasis. The data revealed that overfeeding is accompanied by increased parasympathetic outflow. Typical indices of vagal activity (such as the cephalic insulin release during food ingestion) were increased in all our rat models for hyperphagia. Overfeeding was also accompanied by increased sympathetic tone, reflected by enhanced baseline plasma norepinephrine (NE) levels in both VMH-lesioned animals and rats rendered obese by hyperalimentation. Plasma levels of NE during exercise were, however, reduced in these two groups of animals. This diminished increase in the exercise-induced NE outflow could be normalized by prior food deprivation. It was concluded from these experiments that overfeeding is associated with increased parasympathetic and sympathetic tone. In models for hyperphagia that display a continuously elevated nutrient intake such as the VMH-lesioned and the overfed rat, this increased sympathetic tone was accompanied by a diminished NE response to exercise. This attenuated outflow of NE was directly related to the size of the fat reserves, indicating that the feedback mechanism from the periphery to the central nervous system is altered in the overfed state.

*Cardiovasc Drugs Ther* 1996;10:263-274

**Key Words.** autonomic nervous system, norepinephrine, animal models for obesity, hyperalimentation

The autonomic nervous system plays an important role in the regulation of body processes in health and disease. Data from animal studies reveal, for example, that overfeeding and, in general, obesity (a disproportional increase of the fat mass of the body) are often accompanied by alterations in both sympathetic and parasympathetic functions (8,21,25,26,27). There

might be a causal relationship between the autonomic disturbances and the consequences of overfeeding and obesity. Hyperinsulinemia, for example, can be explained by increased activation of the parasympathetic limb (24,31,32) and/or reduced outflow of the sympathetic branch (8,9,26,62) of the autonomic nervous system. In the present paper the results of a number of studies designed to investigate autonomic functioning in experimentally and genetically hyperphagic rats are discussed. Particular emphasis is given to the relation between overfeeding, autonomic functioning and the processes that are involved in the regulation of peripheral energy substrate homeostasis.

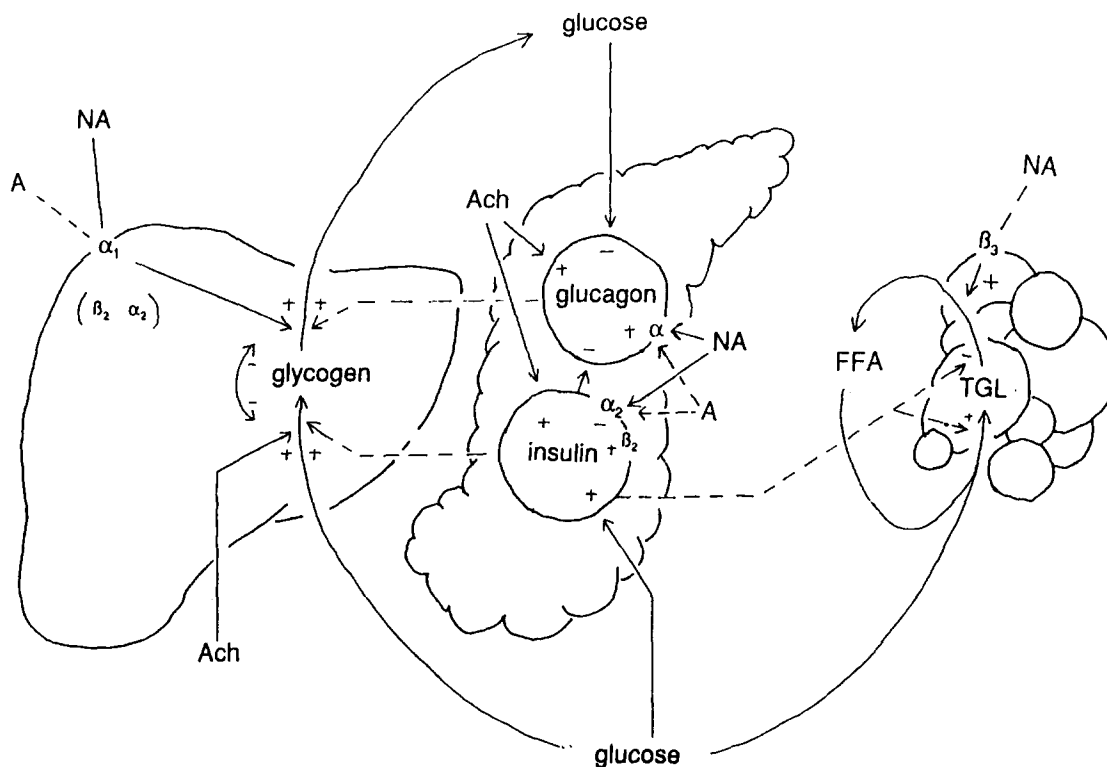
### Autonomic Influences on Energy Substrate Homeostasis

The storage, mobilization and utilization of the different energy substrates is regulated by very sensitive and specific (neuro)hormonal mechanisms. Figure 1 schematically visualizes our present view on the hormonal and neuronal effects on energy substrate homeostasis.

Increased parasympathetic activity leads to the storage of energy substrates such as glucose and free fatty acids (FFA) (for reviews see 17,42,46,59). The main parasympathetic efferents involved in energy substrate homeostasis are those projecting on the liver and the endocrine pancreas. In the liver, stimulation of parasympathetic nerves leads directly to conversion of circulating glucose into glycogen (42). Stimulation of the parasympathetic neurons that enervate the pancreas leads to an increased outflow of insulin by pancreatic  $\beta$ -cells. In turn, insulin lowers blood

Address for correspondence: Anton Scheurink, Department of Animal Physiology, University of Groningen, P.O. Box 14, 9750 AA HAREN, The Netherlands

Received 12 July 1995; accepted in revised form 14 March 1996



**Fig. 1.** Neuronal and hormonal regulation of peripheral energy substrate homeostasis. ACh = acetylcholine, FFA = free fatty acids, NE = norepinephrine, E = epinephrine and TGL = triglycerides.

glucose concentrations via suppression of endogenous glucose production and stimulation of glucose uptake. More specifically, it inhibits hepatic glycogenolysis and gluconeogenesis, and stimulates the storage of glucose in liver in the form of glycogen. In addition, in other insulin-sensitive tissues like resting muscle and adipose tissue, insulin stimulates the uptake, storage and utilization of glucose. Insulin is the only major physiological factor causing a decline in plasma FFA concentrations. It inhibits lipolysis and enhances the re-esterification of FFA by accelerating the transport of glucose into the fat cell.

Activation of the sympathetic branch of the autonomic nervous system leads to the outflow of neuronal norepinephrine (NE, from sympathetic nerve endings) and hormonal epinephrine (E, from the adrenal medulla). Sympathetic activation results in the mobilization of glucose and FFA from the storage tissues (35,42,59,60). The main sympathetic efferents involved in energy substrate homeostasis are travelling through the preganglionic splanchnic nerve and end directly on specific target organs such as liver and pancreas. The effects of E and NE include both direct and indirect actions mediated via  $\alpha$ - and  $\beta$ -adrenoceptor mechanisms. Catecholamines directly enhance hepatic glucose production via stimulation of both glycogenolysis and gluconeogenesis in liver. Catecholamines also limit expenditure of circulating glu-

cose via  $\beta_2$ -adrenoceptor stimulation of muscle glycogenolysis. The  $\alpha_2$ -adrenoceptor mediated inhibition of pancreatic insulin release and  $\alpha$ - and  $\beta$ -adrenergic stimulation of glucagon secretion represent the most important indirect effects of catecholamines on glucose metabolism. Lipolysis is predominantly influenced by neuronal NE (but not physiological doses of E) via activation of  $\beta_3$ -adrenoceptors on the fat cell (18,38). This effect of NE on FFA mobilization is a typical example of a hormonal action of NE since white adipose tissue cells are not directly innervated by sympathetic neurons. Finally, E and NE may stimulate glucose and FFA mobilization indirectly via the  $\alpha_2$ -adrenergic inhibition of insulin release.

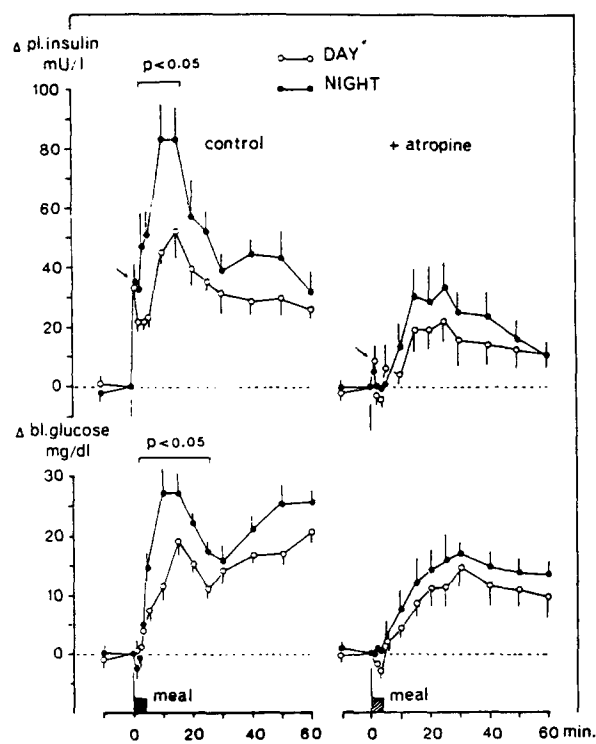
### Energy Substrate Homeostasis and Autonomic Functioning

Activation of one of the two branches of the autonomic nervous system thus leads to alterations in peripheral energy metabolism. One may argue that this relation between autonomic activity and substrate availability must be bidirectional; in other words that changes in the availability of glucose and/or FFA will lead to the activation of one of the two branches of the autonomic nervous system. Indeed, increased availability of energy substrates activates the parasympathetic

branch, while a reduction in the availability of glucose and/or FFA increases sympathetic outflow. Some of the studies from our laboratory providing evidence for this altered autonomic functioning after experimentally-induced changes in glucose and/or FFA homeostasis are described below.

The first set of these experiments focussed on the metabolic and hormonal responses that occur during an increased supply of energy substrates. In these studies, blood samples for measuring blood glucose and plasma insulin concentrations were taken from undisturbed permanently cannulated rats that were subjected to intravenous or intragastric glucose infusion or food intake. Some of the data are presented in Figure 2.

We found that food intake is accompanied by a so-called early insulin response (EIR), an increase in plasma insulin that occurs immediately after the onset of a meal (47,52). This EIR could be suppressed by prior administration of atropine or by subdiaphragmatic vagotomy, providing evidence for a parasympathetic origin of the EIR (11,46,50). Administration of atropine also attenuated and delayed the insulin response to intravenous or intragastric glucose loads (51), which indicates that the parasympathetic nervous system is also involved in the dynamics of insulin secretion during hyperglycemia.



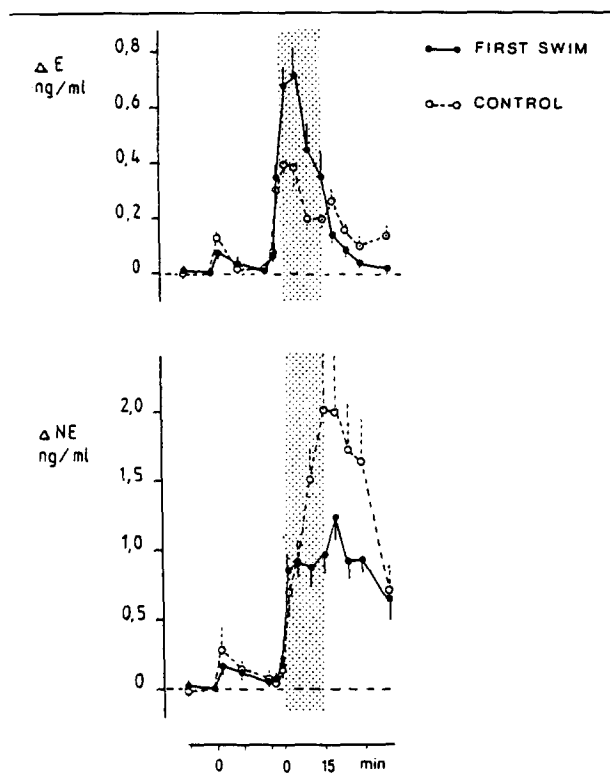
**Fig. 2.** Comparison of plasma insulin and blood glucose responses to food intake between the light and the dark phase with and without premedication with atropine [50].

A second set of experiments dealt with the metabolic and hormonal responses to a reduction in the availability of energy substrates. Hypoglycemic doses of insulin or drugs that block glucose or fatty acid utilization—such as 2-deoxy-D-glucose (2-DG), 2,5-anhydromannitol (2,5 AM) or sodium mercaptoacetate (MA)—were given to permanently cannulated rats. Blood samples were taken during these experiments and (among others) catecholamine responses were measured (34,57). In short, the data revealed that there might be two distinct counterregulatory mechanisms. Activation of the neuronal branch of the sympathetic nervous system (NE) with its direct effects on insulin ( $\downarrow$ ) and glucagon ( $\uparrow$ ) release seems to be the primary neuroendocrine mechanism to compensate for a reduction in energy substrate availability. When this first line of compensatory responses remains insufficient, the adrenomedullary branch (E) is activated as the secondary mechanism (55).

An alternative or additional way to stimulate the mobilization of glucose and FFA is to increase the utilization of these energy substrates. To this end, rats were subjected to exercise, a state in which sympathetic outflow has to alter to increase the flow of glucose and FFA to the exercising muscle. In our model, exercise consists of strenuous swimming against a counter current in a pool with water at 33°C. Blood samples for measuring sympathoadrenal outflow and metabolic hormonal responses were taken before, during and after exercise. The data showed that increased fuel utilization during exercise is accompanied by a stimulation of sympathoadrenal outflow, reflected by elevated plasma NE and E levels (37). The increased catecholamine levels led to an enhanced hepatic glucose production, a reduction in insulin secretion and increased lipolysis (34,38,56). Changes in the experimental conditions (food deprivation, training, MA-treatment, etc) markedly influenced the catecholamine response to exercise (57).

One example is given in Figure 3: the first time swimming (emotional stress) was characterized by a high E response and relative low NE levels. In contrast, well-accustomed animals showed a definite NE response with low E concentrations. This suggests that emotional stress shifts the sympathoadrenal response to swimming from NE to E (39). This shift is accompanied by attenuated lipolysis and increased glucose mobilization (39). Since glucose serves as the predominant fuel for the brain, this increased glucose mobilization can be seen as an appropriate and functional response to an uncontrollable stressor, because it guarantees an adequate supply of glucose to the central nervous system under stressful conditions.

We concluded from these data that the two branches of the sympathoadrenal system are both functionally and metabolically dissociated. Further studies in our laboratory revealed that this regulation of sympathetic outflow may take place at many levels in the sympathetic nervous system (35). Local infu-



**Fig. 3.** Plasma epinephrine (E) and norepinephrine (NE) responses to exercise in naive (first swim) and well-accustomed control rats. Exercise indicated by the dotted period [39].

sions of adrenergic and serotonergic agonists and antagonists into several hypothalamic areas identified the hypothalamus as a major center in the brain coordinating sympathoadrenal outflow and energy homeostasis (40,41,44). Experiments in which selective adrenoceptor agonists and antagonists were intravenously infused in exercising rats showed that presynaptic regulatory mechanisms acting at sympathetic nerve terminals may determine the ultimate sympathetic activation of the different target organs involved in energy homeostasis (37,38).

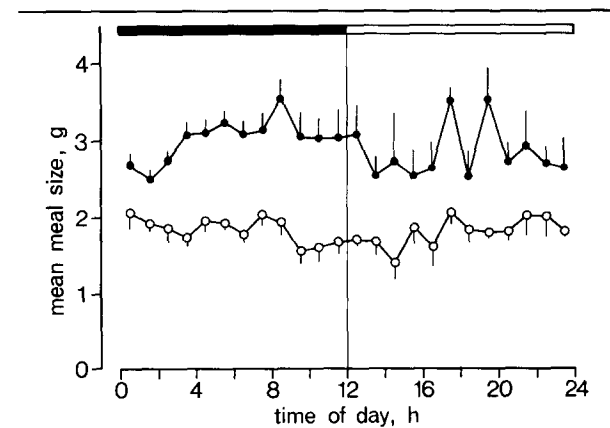
### Animal Models for Hyperphagia

The major aim of the present paper is to focus on the relation between overfeeding, autonomic functioning and the processes that are involved in the regulation of peripheral energy substrate homeostasis. In our laboratory, four animal models for hyperphagia are used through the last decennia: the genetically obese Zucker rat, the VMH-lesioned rat, the LH-stimulated rats and, more recently, rats rendered obese by hyperalimantation. The Zucker rat and hypothalamically-manipulated rats are the most studied animal models for hyperphagia and obesity (8,49), the hyperalimanted rat model was specially developed in our laboratory (5). Some of the typical characteristics of these different animal models are described below.

The Zucker fa/fa "fatty" rat is a classic genetic rat model for obesity (for reviews see 8,9,21,49). It is a spontaneous genetic abnormality, discovered by Zucker and Zucker (62) in their colony of Wistar rats. Obesity occurs along predictable genetic Mendelian lines associated with a single recessive gene. Hyperphagia is one of the main characteristics of the fatty Zucker rat. Feeding studies in our laboratory revealed that obese Zucker rats eat more than their lean littermates, especially in the phase of the light dark cycle (1).

The higher food intake is mainly caused by a dramatic increase in meal size (Figure 4) and a small reduction in meal frequency (1). Metabolic elements of the Zucker syndrome includes a.o. hyperinsulinemia, hyperglyceridemia and insulin resistance (13,19,20,54). Anatomical studies revealed that pancreatic beta cells and white adipocytes are increased in size and number (2,14). Furthermore, thermogenic defects, reduced metabolic rate, a disturbed HPA-axis and decreased locomotor activity are also reported in the fa/fa rat (16,49,53).

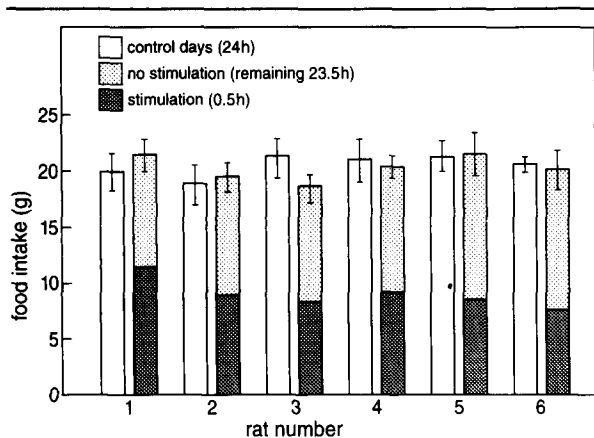
The hyperphagic animal that results from a surgical perturbation of the ventromedial nucleus of the hypothalamus (VMH) is by far the most studied non-genetic model for obesity. Lesions in the VMH, either electrolytic, radio-frequency or chemical, and knife cuts around the VMH all result in varying degrees of hyperphagia and weight gain (for reviews see 8,49). Hyperphagia is the result of an increase in meal size but not meal frequency. The normal day-night cycle seems to disappear in VMH-lesioned animals, resulting in overfeeding during the light period combined with a somewhat reduced food intake in the dark period (49). However, unpublished studies from our laboratory in which very discrete lesions were applied in the ventrolateral part of the VMH reveal that hyperphagia can also occur without any changes in the circadian rhythmicity. Metabolic features of the VMH



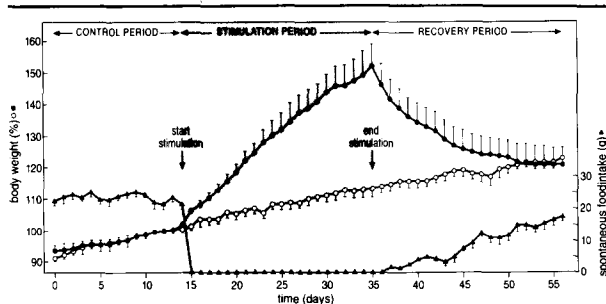
**Fig. 4.** Mean meal size (g) per hour over the whole light-dark cycle for lean and obese Zucker rats (mean  $\pm$  SEM).  $\circ$  = lean,  $\bullet$  = obese [1].

syndrome includes hyperinsulinemia in the face of normoglycemia, hypertriglyceridemia, decreased glucagon and growth hormone levels, adiposity and reduced energy expenditure which seems primarily the reflection of decreased brown adipose tissue thermogenesis (3,8,49).

Electrical stimulation of the lateral hypothalamic area (LHA) also induces excessive eating in the rat. In this type of hyperphagic rat, baseline blood glucose and plasma insulin levels are above normal (43,45). The LHA-stimulated rats cease to eat voluntarily in between stimulation/feeding sessions (43). Moreover, after termination of the daily LHA stimulations—when the rats have become obese—they spontaneously limit food intake until their body weight reaches normal control values (Figure 5a and b). During this voluntary aphagia, blood glucose immediately drops below control levels. The decline in baseline insulin levels is much slower (43).



**Fig. 5a.** Comparison of food intake on control days without stimulation (twelve sessions) versus stimulation (eighteen sessions) of six rats with permanent electrodes implanted in the lateral hypothalamus. Food was available ad lib during 30 min stimulation periods and during the rest of the day. Vertical lines represent SEM [45].



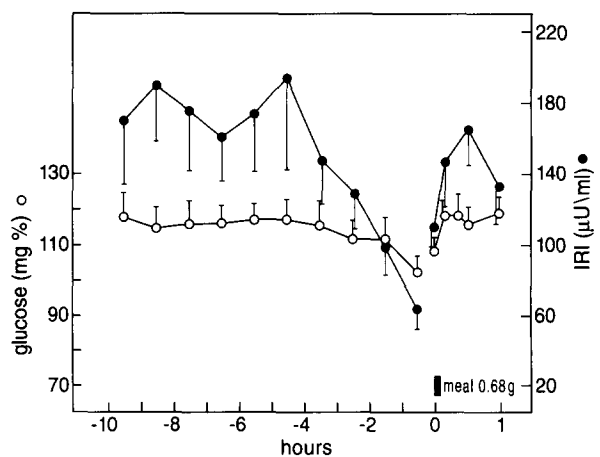
**Fig. 5b.** Mean and SEM of body weight (○) and spontaneous food intake (■) of eight rats subjected from days 5 to 35 to three daily sessions of electrical LHA stimulation. For comparison mean body weight of four non-stimulated controls (○) is added [43].

It is interesting to note that the first voluntary meals after termination of LHA stimulation coincide with the return of baseline insulin to the normal control value (Figure 5c). This observation may be used as circumstantial evidence for a role of insulin in the control of feeding behavior (7). Further information on other metabolic characteristics of the LHA-stimulation-syndrome is scarce.

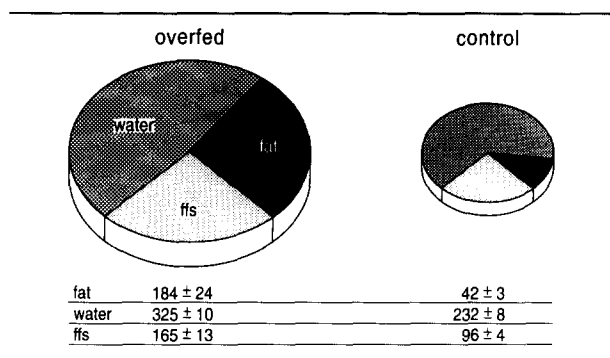
The final and most recent model for hyperphagia, the hyperalimmented rat, was developed by Börk Balkan during his PhD-study in Groningen (5). In this model, rats are subjected to intragastric overfeeding for 35 days. For this purpose, a diet (liquid diet prepared from Nutrison powder) is infused through a permanent implanted intragastric cannula at a rate of 0.3 mL/min during twelve 30-minutes periods at the end of the light cycle and during the night. The diet is delivered in the light period at 60-minute intervals between the infusion periods. Total daily caloric intake during overfeeding is about twice the amount of that under the ad libitum condition. Hyperalimmented rats display a strongly increased body weight (674 gram vs 370 gram in controls) and altered body composition (Figure 6). These rats have elevated plasma levels of FFA and enlarged fat pads. This form of overfeeding is also accompanied by hyperinsulinemia and normoglycemia, indicating a progressive insulin insensitivity induced by excessive nutrient supply (5).

### Autonomic Functioning and Metabolic Consequences in Hyperphagic Rats

Symptoms of experimental and genetic hyperphagia, e.g., obesity, adiposity and hyperinsulinemia, are generally accompanied by profound changes in autonomic



**Fig. 5c.** Blood glucose and plasma insulin levels before, during and after the first voluntary meal after a LHA stimulation session [43].



**Fig. 6.** Body weight composition during hyperalimentation of overfed rats and lean controls after 35 days of intragastric overfeeding. Averages  $\pm$  SEM [5].

functioning (8,21,26,27). Several authors suggest a causal relationship between these symptoms and altered autonomic functioning in which, for example, hyperinsulinemia can be explained by increased activation of the parasympathetic nervous system (24, 32,33) and/or reduced sympathetic outflow (8,26). In the following paragraphs several aspects of autonomic (dys)functioning and the consequences for peripheral energy substrate homeostasis in the abovementioned animal models for hyperphagia (and especially the hyperalimented rat) will be discussed.

Several studies suggest a direct relationship between hyperphagia, obesity and increased parasympathetic tone (20,21,24,31,33,53). The fatty Zucker rat, for example, shows a number of metabolic disorders pointing to a permanent change in the function of parasympathetic nervous system. Elevated plasma insulin levels and reduced baseline heart rate (Tables 1 and 2,29) reflect increased parasympathetic tone. Furthermore, data from young fatty Zucker rats reveal that the development of hyperinsulinemia is primarily the result of increased parasympathetic activity (24,32,33,53). The vagally mediated cephalic insulin release during food ingestion is also markedly enhanced in young fatty Zucker rats (19,20,31). However, we found that typical vagal responses, such as

**Table 1.** Baseline values of plasma insulin ( $\mu$ U/ml) in three different animal models for obesity

	Plasma insulin ( $\mu$ U/ml)	n
obese Zucker	309 $\pm$ 28*	7
lean Zucker	34 $\pm$ 3	7
VMH-lesioned	128 $\pm$ 4*	6
control	48 $\pm$ 2	7
overfed	102 $\pm$ 6*	7
control	44 $\pm$ 2	12

Values are averages  $\pm$  SE and measured in the permanently cannulated undisturbed animal in his own home cage. \*Denotes a significant difference from their lean littermates ( $p < 0.05$ ).

**Table 2.** Baseline values of blood glucose, plasma insulin, epinephrine (E), and norepinephrine (NE) in obese and lean 10–12 month old Zucker rats

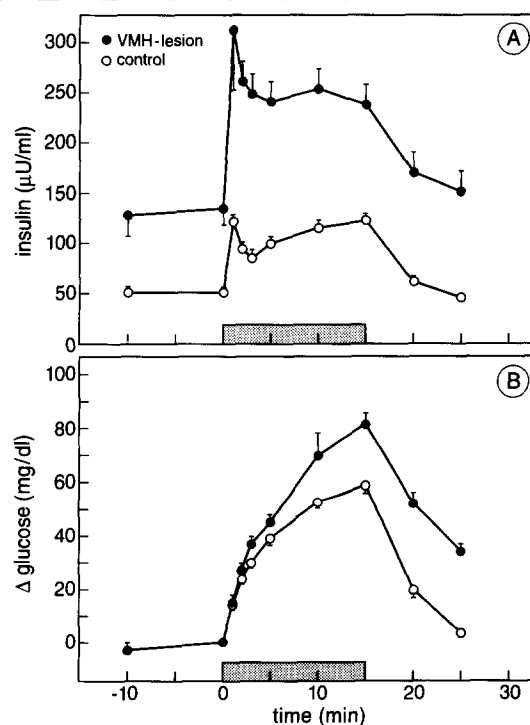
	n	Blood glucose (mg/dl)	Plasma insulin ( $\mu$ U/ml)	Plasma E (pg/ml)	Plasma NE (pg/ml)
obese	14	122 $\pm$ 2*	287 $\pm$ 26*	46 $\pm$ 8	352 $\pm$ 36
lean	14	116 $\pm$ 3	30 $\pm$ 2	68 $\pm$ 8	288 $\pm$ 22

Values are averages  $\pm$  SE, measured at in the home cage of the animals.

\*Denotes a significant difference ( $P < 0.05$ ) between obese and lean rats.

the cephalic insulin release or bradycardia in a conditioned fear situation, do not occur in much older (10–12 month old) obese Zucker rats.

In the VMH-lesioned rat, an increased insulin release can be observed during the so-called dynamic phase of the VMH-syndrome (3) (Figure 7). Data on the vagal activity during the static phase of the VMH-syndrome are somewhat conflicting. Both an increased vagally-induced gastric acid secretion (58) as well as a complete disappearance of the cephalic phase insulin release (49) are described for VMH-lesioned animals. One may hypothesize that increased parasympathetic responsiveness is mainly associated with early stages of hyperphagia in the Zucker and the VMH-lesioned rat, and that vagal responses are reduced at an older age. This may be caused by altered



**Fig. 7.** Plasma insulin profiles in blood glucose in VMH-lesioned rats (●) and controls (○) before, during and after IV glucose infusion. The infusion period is indicated by a horizontal bar. Values represent means  $\pm$  SEM [3].

central parasympathetic drive. Finally, it has to be mentioned that the absence of the preabsorptive insulin response combined with increased baseline insulin concentrations may also be explained as a combined consequence of increased vagal activity at a younger age and insulin insensitivity during the increase in fat mass during the late phase of obesity (13,14,21,22,28,54). Increased insulin insensitivity may also explain the elevated baseline insulin levels and the exaggerated insulin response to a glucose infusion in the rats rendered obese by hyperalimentation (5).

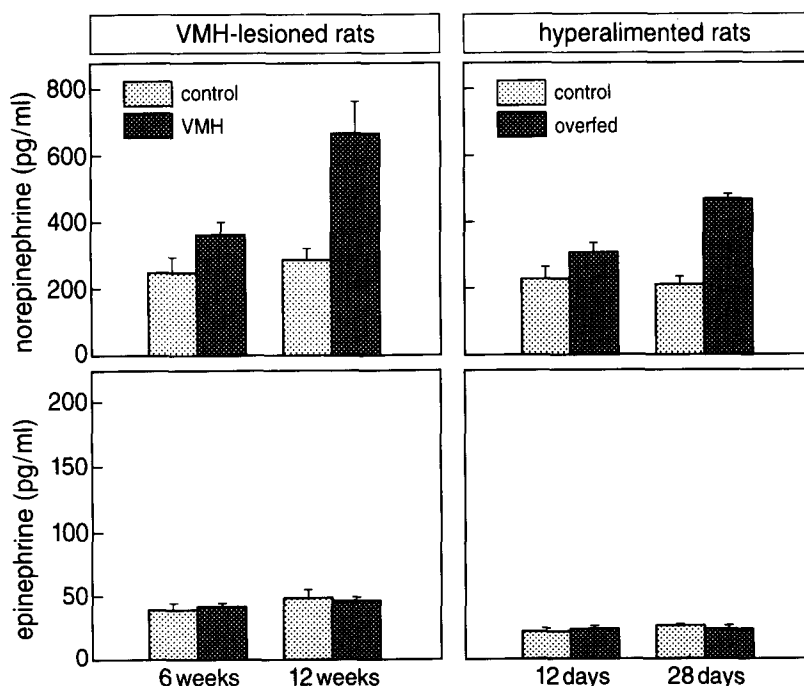
Several studies suggested that diminished sympathoadrenal activity rather than increased parasympathetic responsiveness might contribute to the metabolic deficiencies during obesity and hyperphagia (8,9,26,61). To test this hypothesis, we investigated whether hyperphagia related changes in three of our animal models might be accompanied by reduced sympathetic functioning in rest and exercise. The data revealed that overfeeding is indeed characterized by a reduced sympathetic activity during exercise but that sympathetic outflow is enhanced under baseline conditions (3,4,5,6) (Figure 8).

The increased baseline outflow—leading to increased mobilization of energy substrates (reflected by slightly enhanced blood glucose levels in obese Zucker rats [Table 3]) and increased metabolic rate—may be viewed as a counterregulatory response to the increased fat and glycogen stores in overfeeding.

Whether the elevated NE concentrations in overfeeding are indeed the consequence of enhanced release of NE in brown adipose tissue or liver is unknown. In any case, in humans it is well documented that continuously elevated plasma NE levels in combination with the insulin resistance in overfeeding might constitute a risk for high blood pressure, atherosclerosis, etc (10,12,15,23,30,48).

Stimulated NE outflow was attenuated in VMH-lesioned animals and in rats rendered obese by hyperalimentation (4,5). Figure 9 shows the attenuated NE response to exercise in the hyperalimented animals. In the VMH-lesioned animals, this diminished increase in NE outflow could be normalized by prior food deprivation (6). The exercise-induced changes in the 10–12 month old obese Zucker rats were no different from their lean littermates, suggesting that the central and descending pathways for sympathoadrenal activation are seemingly intact in this form of genetic hyperphagia (36).

The changes in autonomic outflow in the abovementioned experiments were accompanied by marked alterations in peripheral energy homeostasis. A few examples of these metabolic changes are listed below. First, baseline levels of plasma FFA were increased in all types of overfeeding. These increased baseline levels of FFA were accompanied by an attenuated FFA response to exercise (4,5,36), probably caused by a decreased sensitivity of white adipose tissue to



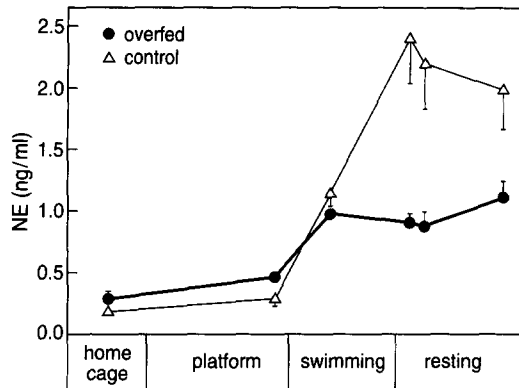
**Fig. 8.** Baseline plasma epinephrine and norepinephrine levels in VMH-lesioned, hyperalimented and control rats. Data from [3,4,5].



**Table 3.** Changes in obesity in three animal rat models and man

	Zucker fa/fa rat	VMH-lesioned rat	Hyperalimmented rat	Human obesity
hyperphagia	+	+	+	+
hyperinsulinemia	+	+	+	+
insulin resistance	+	+	+	+
energy expenditure	↓	↓	↓	↓ *1
locomotor activity	↓	↓	↓	↓
vagal tone	↑	↑	?	?
vagal responses	↑ young ↓ 10–12 months	↑ dynamic phase ↓ static phase	↓	?
sympathetic tone	↑	↑	↑	↑
sympathetic responses	↓	↓	↓	↓
adrenoceptor sensitivity	↓	↓	↓	↓

\*1: decreased energy expenditure does generally but not always occur in human obesity.

**Fig. 9.** Plasma NE response to exercise in hyperalimmented (●) and control rats (○) [5].

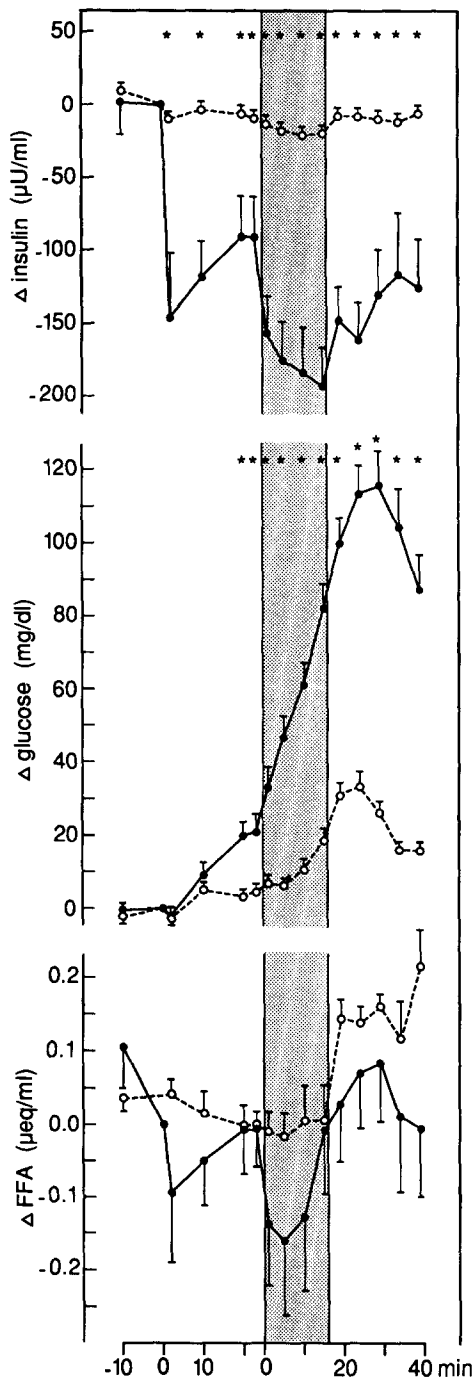
noradrenergic stimulation. In the VMH-lesioned and the overfed rats, the reduction of the exercise-induced increase in plasma FFA can also be explained, in part, by the diminished NE response during exercise (3,5). The normal reduction in insulin release during exercise did not occur in the overfed rats. In the Zucker and the VMH-lesioned rats, the exercise-induced changes in plasma insulin were (in percent) similar to those in control animals. Blood glucose responses to exercise but also E infusion (3,4,5,36) were highly increased in all animal models for hyperphagia. This exaggerated increase of blood glucose can only be explained by dramatic changes in postsynaptic receptor function. Increased  $\alpha_1$  and/or  $\beta_2$ -adrenoceptor sensitivity during the development of obesity, leading to increased hepatic glucose production ( $\alpha_1$ -adrenoceptors, 28) and reduced glucose uptake caused by increased muscle glycogenolysis ( $\beta_2$ -adrenoceptors, 22), may have caused the enhanced blood glucose levels.

## Conclusions

The observations reviewed in this paper clearly demonstrate that metabolic needs are regulated via the activity of the autonomic nervous system. In turn, metabolic states profoundly determine the functioning of the autonomic regulatory mechanisms. Hyperphagia results in altered functioning of both sympathetic and parasympathetic branches of the autonomic nervous system, both at central and peripheral levels.

The present data add to the hypothesis that the feedback mechanisms which may provide the central nervous system with information on the size of the peripheral energy stores are altered in the hyperphagic state. In models for hyperphagia that display a continuously elevated nutrient intake such as the VMH-lesioned and the overfed rat, the diminished sympathetic response seems to be linked to a positive energy balance. The reinstallation of a normal NE-response to exercise in 48h-fasted animals VMH-lesioned animals (6) supports this hypothesis. In genetically obese animals, an impaired nutrient mobilization and a disturbed feedback mechanism to the areas in the brain that regulate autonomic functioning might be the underlying factor to the hyperphagia, explaining the seemingly normal catecholamine response to exercise in these animals. The hypothesis that exaggerated endogenous energy availability is responsible for the reduced NE response also appears to hold for baseline plasma NE concentrations. Overfed and VMH-lesioned animals reveal elevated baseline NE levels, whereas fatty Zucker rats do not (3,5,36). These continuously elevated plasma NE levels during overfeeding might, in the human situation, constitute a risk for cardiovascular diseases (10,28,30).

Finally, it is obvious that hyperphagia/obesity cannot be viewed as a uniform phenomenon. Rather it



**Fig. 10.** Blood glucose, plasma free fatty acids and insulin concentration before, during, and after exercise in obese (●—●) and lean (○—○) Zucker rats. Data from glucose, FFA and insulin are expressed as average changes  $\pm$  SEM from baseline levels [36].

is a state of the organism in which disturbances in regulatory mechanisms are differentially affected by factors like overeating or the genetic make-up of the animal. In addition, the duration of the overfeeding and/or the factor age is an important variable both in terms of autonomic regulation and risk factor for various (psycho)somatic diseases.

## References

1. Alingh Prins A, de Jong-Nagelsmit A, Keyser J, Strubbe JH. Daily rhythms of feeding in the genetically obese and lean Zucker rats. *Physiol Behav* 1986;38:423-426.
2. Bass S, Ritter S. Decreased beta-adrenergic receptor binding in obese female Zucker rats. *J Auton Nerv System* 1985; 14:81-87.
3. Balkan B, Steffens AB, Bruggink JE, Strubbe JH. Hyperinsulinemia and glucose tolerance in obese rats with lesions of the ventromedial hypothalamus: dependence on food intake and route of administration. *Metabolism* 1991;40: 1092-1100.
4. Balkan B, Strubbe JH, Bruggink JE, Steffens AB. Altered sympathetic control of nutrient mobilization during physical exercise after lesions in the VMH. *Am J Physiol* 1991;260: R368-372.
5. Balkan B, Strubbe JH, Bruggink JE, Steffens AB. Overfeeding-induced obesity in rats: insulin sensitivity and autonomic regulation of metabolism. *Metabolism* 1993;42: 1509-1518.
6. Balkan B, van Dijk G, Strubbe JH, Bruggink JE, Steffens AB. Exercise-induced sympathetic FFA mobilization in VMH-lesioned rats is normalized by fasting. *Am J Physiol* 1992;262:R981-985.
7. Baskin DG, Figlewicz DP, Woods SC, Porte Jr D, Dorsa DM. Insulin in the brain. *Ann Rev Physiol* 1987;49:335-347.
8. Bray GA, York DA. Hypothalamic and genetic obesity in experimental animals: An autonomic and endocrine hypothesis. *Physiol Rev* 1979;59:719-809.
9. Bray GA, York DA, Fisler JS. Experimental obesity: A homeostatic failure due to defective nutrient stimulation of the sympathetic nervous system. IN: *Vitamins and hormones*, New York: Academic press; 1989:1-125.
10. Brindley DN, Rolland Y. Possible connections between stress, diabetes, obesity, hypertension and altered lipoprotein metabolism that may result in atherosclerosis. *Clin Sci* 1989;5:453-463.
11. Buwalda B, Strubbe JH, Hoes MHW, Bohus B. Reduced preabsorptive insulin response in aged rats: differential effects of amphetamine and arginine-vasopressin. *J Auton Nerv Syst* 1991;36:123-128.
12. Chiang B, Perlman LV, Epstein FH. Overweight and hypertension, a review. *Circulation* 1969;39:403-421.
13. Crettaz M, Prentki M, Zaninetti D, Jeanrenaud B. Insulin resistance in soleus muscle from obese Zucker rats. *Biochem J* 1980;186:525-534.
14. Cushman SW, Zarnowski MJ, Franzusoff AJ, Salans LB. Alterations in glucose metabolism and its stimulation by insulin in isolated adipose cells during the development of genetic obesity in the Zucker fatty rat. *Metabolism* 1978; 27:1930-1940.
15. Dustan HP. Mechanisms of hypertension associated with obesity. *Ann Intern Med* 1983;98:860-864.

16. Guillaume-Gentil C, Rohner-Jeanrenaud F, Abramo F, Bessetti GE, Rossi GL, Jeanrenaud B. Abnormal regulation of the hypothalamo-pituitary-adrenal axis in genetically obese fa/fa rat. *Endocrinology* 1990;126:1873-879.
17. Havel P, Taborsky Jr GJ. The contribution of the autonomic nervous system to changes of glucagon and insulin secretion during hypoglycemic stress. *Endocrine Rev* 1989;10:332-350.
18. Hollenga C, Zoagmsa J. Direct evidence for the atypical nature of functional  $\beta_3$  adrenoceptor. *Br J Pharmacol* 1989;98:1420-1424.
19. Ionescu E, Rohner-Jeanrenaud F, Proietto J, Rivest RW, Jeanrenaud B. Taste-induced changes in plasma insulin and glucose turnover in lean and genetically obese rats. *Diabetes* 1988;37:773-779.
20. Ionescu E, Sauter JF, Jeanrenaud B. Abnormal oral glucose tolerance in genetically obese (fa/fa) rats. *Am J Physiol* 1985;248:E500-506.
21. Jeanrenaud B, Halimi S, Van de Werve G. Neuro-endocrine disorders seen as triggers of the triad: obesity—insulin resistance—abnormal glucose tolerance. *Diabet Metab Rev* 1985;1:261-281.
22. Kemmer FW, Berger M, Herberg L et al. Glucose metabolism in perfused skeletal muscle. Demonstration of insulin resistance in the obese Zucker rats. *Biochem J* 1979;178:733-741.
23. Lavie CJ, Messerli FM. Cardiovascular adaptation of obesity and hypertension. *Chest* 1986;90:275-279.
24. Lee HC, Curry DL, Stern JS. Direct effect of CNS on insulin hypersecretion in obese Zucker rats: involvement of vagus nerve. *Am J Physiol* 1989;256:E439-444.
25. Levin BE, Stoddard-Apter S, Sullivan AC. Central activation and peripheral function of sympathoadrenal and cardiovascular systems in the Zucker rat. *Physiol Behav* 1984;32:295-299.
26. Levin BE, Triscari J, Sullivan AC. Abnormal sympathoadrenal function and plasma catecholamines in obese Zucker rats. *Pharmacol Biochem Behav* 1980;13:107-113.
27. Martin RJ, Harris RBS, Jones DD. Evidence for a central mechanism of obesity in the Zucker fatty rat. *Proc Soc Exp Biol Med* 1986;183:1-10.
28. Modan M, Halkin H, Almog S et al. Hyperinsulinemia—a link between obesity and glucose tolerance. *J Clin Invest* 1985;75:809-817.
29. Nyakas C, Prins AJA, Bolus B. Age related alterations in cardiac response to emotional stress: relations to behavioral reactivity in the rat. *Physiol Behav* 1990;47:273-280.
30. Reaven PD, Barretonnour EL, Browner DK. Abnormal glucose tolerance and hypertension. *Diabet Care* 1990;13:119-125.
31. Rohner-Jeanrenaud F, Hochstrasser AC, Jeanrenaud B. Hyperinsulinemia of preobese fa/fa rats is partly vagus nerve mediated. *Am J Physiol* 1983;244:E317-322.
32. Rohner-Jeanrenaud F, Ionescu E, Jeanrenaud B. The origins and role of efferent vagal nuclei in hyperinsulinemia in hypothalamic and genetically obese rodents. *J Auton Nerve System* 1983;9:173-184.
33. Rohner-Jeanrenaud F, Jeanrenaud B. Vagal mediation of corticotropin-releasing factor-induced increase in insulinemia in lean and genetically obese fa/fa rats. *Neuroendocrinology* 1980;52:52-56.
34. Scheurink A, Ritter S. Sympathoadrenal responses to glucoprivation and lipoprivation in rats. *Physiol Behav* 1993;53:995-1000.
35. Scheurink AJW, Steffens AB. Central and peripheral control of sympathoadrenal activity and energy metabolism in rats. *Physiol Behav* 1990;48:909-920.
36. Scheurink AJW, Steffens AB, Balkan B, Roossien A. Sympathoadrenal function in 10-12 months old genetically obese Zucker rats. *Physiol Behav* 1992;52(4):679-685.
37. Scheurink AJW, Steffens AB, Bouritius H, et al. Adrenal and sympathetic catecholamines in exercising rats. *Am J Physiol* 1989;256:R155-160.
38. Scheurink AJW, Steffens AB, Bouritius H, et al. Sympathoadrenal influence on glucose, FFA, and insulin levels in exercising rats. *Am J Physiol* 1989;256:R161-168.
39. Scheurink AJW, Steffens AB, Dreteler GH, Benthem L, Bruntink R. Experience affects exercise-induced changes in catecholamines, glucose, and FFA. *Am J Physiol* 1989;256:R169-173.
40. Scheurink AJW, Steffens AB, Gaykema RPA. Hypothalamic adrenoceptors mediate sympathoadrenal activity in exercising rats. *Am J Physiology* 1990;259(28):R470-R477.
41. Scheurink AJW, Steffens AB, Gaykema RPA. Paraventricular hypothalamic adrenoceptors and energy metabolism in exercising rat. *Am J Physiology* 1990;259(28):R478-R484.
42. Shimazu T. Neural control of intermediate metabolism. IN: Lightman S, Everitt B, eds. *Neuroendocrinology*. Oxford: Blackwell, 1986:309-334.
43. Steffens AB. Influence of reversible obesity on eating behavior, blood glucose and insulin in the rat. *Am J Physiol* 1975;228:1738-1744.
44. Steffens AB, Damsma G, van der Gugten J, Luiten PGM. Circulating free fatty acids, insulin, and glucose during chemical stimulation of the lateral and ventromedial areas of the hypothalamus in the rat. *Am J Physiol* 1984;247:E765-771.
45. Steffens AB, Mogenson GJ, Stevenson. Blood glucose, insulin and free fatty acids after stimulation and lesions of the hypothalamus. *Am J Physiol* 1972;222:1446-1452.
46. Steffens AB, Strubbe JH, Balkan B, Scheurink AJW. Neuroendocrine mechanisms involved in regulation of body weight, food intake and metabolism. *Neurosci Biobehav Rev* 1990;14:305-313.
47. Steffens AB, van der Gugten J, Godeke J, Luiten PGM, Strubbe JH. Meal-induced increases in parasympathetic and sympathetic activity elicits simultaneous rises in plasma insulin and free fatty acids. *Physiol Behav* 1986;37:119-122.
48. Stolar MW. Atherosclerosis in diabetes; the role of hyperinsulinemia. *Metabolism* 1988;37:suppl 1,1-9.
49. Storlien, LH. Animals models of obesity. In: *Animal models in psychopathology*. Academic Press, Australia. pp. 147-176, 1984.
50. Strubbe JH. Parasympathetic involvement in rapid meal-associated conditioned insulin secretion in the rat. *Am J Physiol* 1992;263:R615-618.
51. Strubbe JH, Bruggink JE, Steffens AB. Cholinergic potentiation of the intermediate insulin response to glucose and food intake. *Diabetologia* 1990;33:A27.
52. Strubbe JH, Steffens AB. Rapid insulin release after ingestion of a meal in the unanesthetized rat. *Am J Physiol* 1975;229:1019-1022.
53. Stubbs M, York DA. Central glucocorticoid regulation of parasympathetic drive to pancreatic B-cells in the obese fa/fa rat. *Int J Obesity* 1991;15:547-554.
54. Terrettaz J, Jeanrenaud B. In vivo hepatic and peripheral insulin resistance in genetically obese (fa/fa) rats. *Endocrinology* 1983;112:1346-1351.

55. Van Dijk G. Central and peripheral mechanisms involved in fuel homeostasis. *Thesis*. University of Groningen, 1995.
56. Van Dijk G, Balkan B, Lindtfeldt J, et al. Contribution of liver, glucagon, and adrenaline to the glycaemic response to exercise in rats. *Acta Physiol Scand* 1994;150:305–313.
57. Van Dijk G, Scheurink AJW, Ritter S, Steffens AB. Glucose homeostasis and sympathoadrenal activity in mercaptoacetate-treated rats. *Physiol Behav* 1995;57:759–764.
58. Weingarten WP, Powley TL. Pavlovian conditioning in the cephalic phase of gastric acid secretion in the rat. *Physiol Behav* 1981;27:217–221.
59. Woods SC, Taborsky Jr GJ, Porte D. CNS control of nutrient homeostasis. IN *Handbook of Physiology: The nervous system Intrinsic regulatory systems in the brain*. Bethesda, MD: Am. Physiol Soc, 1986; sect. 1, vol IV, chapt. 7 p. 365–412.
60. Yamaguchi N. Sympathoadrenal system in neuroendocrine control of glucose mechanisms involved in the liver, pancreas, and adrenal gland under hemorrhagic and hypoglycemic stress. *Can J Physiol Pharmacol* 1992;70:167–206.
61. York DA, Marchington D, Holt SJ, Allars I. Regulation of sympathetic activity in lean and obese Zucker (fa/fa) rats. *Am J Physiol* 1985;249:E299–305.
62. Zucker LM, Zucker TF. Fatty, a new mutation in the rat. *J Heredity* 1961;52:275–278.